Journal of the Neurological Sciences 332 (2013) 121–127

Contents lists available at SciVerse ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

A 10-year follow-up of a population-based study of people with multiple sclerosis in Stockholm, Sweden: Changes in disability and the value of different factors in predicting disability and mortality

Charlotte Chruzander [a,b,c,*], Sverker Johansson [a,b,c], Kristina Gottberg [a,b], Ulrika Einarsson [a,b,c], Sten Fredrikson [b], Lotta Widén Holmqvist [a,b,c], Charlotte Ytterberg [a,b,c]

[a] Karolinska Institutet, Department of Neurobiology, Care Sciences and Society, Huddinge, Sweden
[b] Karolinska Institutet, Department of Clinical Neuroscience, Stockholm, Sweden
[c] Karolinska University Hospital, Department of Physical Therapy, Stockholm, Sweden

ARTICLE INFO

Article history:
Received 18 March 2013
Received in revised form 5 July 2013
Accepted 8 July 2013
Available online 26 July 2013

Keywords:
Multiple sclerosis
Longitudinal
Functioning
Disability
Prognostic factors
Epidemiology

ABSTRACT

Background: Most people with multiple sclerosis (PwMS) experience progressively worsening disability over a period of decades, thus further knowledge about the long-term changes in different areas of disability is essential.
Objectives: The aims of this study were to evaluate changes in disability over ten years in PwMS, and to explore the value of personal and disease-specific factors and depressive symptoms in predicting disability. A further aim was to explore the value of these factors as predictors of mortality.
Methods: This study was based on a 10-year follow-up of a population-based study in Stockholm (n = 166). Home visits were used to collect data on personal and disease-specific factors, walking ability, manual dexterity, cognitive function, mood, activities of daily living (ADL) and social/lifestyle activities.
Results: The proportion of the study population who had disability in cognition, mood and social/lifestyle activities remained stable, while the proportion with disability in walking, manual dexterity and ADL increased. Disease severity predicted an increase in all studied variables of disability except in depressive symptoms. Older age and depressive symptoms were associated with mortality.
Conclusion: This study illustrates the importance of tailored interventions for PwMS and highlights the need for health-care professionals to consider the psychological aspects of the disease. Furthermore, our results indicate that the Expanded Disability Status Scale was a useful tool for predicting future disability.

1. Introduction

Multiple sclerosis (MS) is a neuroinflammatory and neurodegenerative disease which has a variable course in different individuals over the course of several decades [1]. Even though disability in people with MS (PwMS) often occurs in many areas of functioning [2], population-based long-term follow-ups (10 years or more) of PwMS often focus on changes in overall scores of disease severity [3], assessed by the Expanded Disability Status Scale (EDSS) [4]. Long-term follow-ups of other impairments often study only one impairment, e.g., cognition, are based on selected cohorts, and the follow-up period is often less than a decade [5]. Age, the type of MS and the type of symptoms at onset, as well as sex and the degree of remission after the first bout have all been found to be valuable predictors of long-term disease progression, as assessed by the EDSS [6]. Factors that can predict disability in specific areas are rare.

The influence of age at diagnosis, sex and disease-specific factors on mortality in PwMS has been well studied [7]; however, the influence of personal factors such as coping capacity and level of education is unknown. Depressive symptoms are associated with impaired cognition, decreased frequency of social/lifestyle activities and limitations in the ability to work [8]; however, the value of depressive symptoms in predicting long-term disability and mortality requires exploration. In addition, considering the high prevalence of cognitive impairment in PwMS [5], it is important to study whether there is an association between cognitive impairment and mortality.

In order to prioritise different treatment options and provide tailored interventions, knowledge resulting from longitudinal population-based studies which take into account the complex relationship between health, disability, and personal and environmental factors [9] is required. Hence, the aims of this study were to explore changes in disability in a 10-year follow-up of a population-based cohort of PwMS, and to

* Corresponding author at: Division of Neurology, R54, Karolinska University Hospital, Huddinge, SE-141 86 Stockholm, Sweden. Tel.: +46 8 585 822 77; fax: +46 8 774 4822.
E-mail address: charlotte.chruzander@ki.se (C. Chruzander).

0022-510X
http://dx.doi.org/10.1016/j.jns.2013.07.003

explore the value of personal and disease-specific factors and depressive symptoms as predictors of disability. A further aim was to explore the value of personal and disease-specific factors, depressive symptoms and cognitive impairment as predictors of mortality.

2. Materials and methods

2.1. Participants

This study is based on a 10-year follow-up of a population-based study in Stockholm, Sweden, the recruitment process of which has been described in detail previously [10]. In brief, the PwMS included at baseline (from September 1999 to September 2002) were recruited from a temporary data pool consisting of 2129 patients from all hospital neurology clinics in Stockholm County, in order to obtain the highest possible population-based ascertainment. A random sample was drawn, representing 15% (n = 321) of the data pool. Inclusion criteria were: a definite and informed diagnosis of MS, being a resident in Stockholm County and having no diagnosis of other severe neurological or psychiatric illness. Of the 196 PwMS who fulfilled the inclusion criteria, 166 (85%) gave informed consent and agreed to participate. In order to collect data for the 10-year follow-up, the same PwMS were identified and those still alive were contacted by post.

2.2. Data collection

Data collection was performed by home visits at a date 10 years ± 6 months after baseline (from May 2009 to February 2012). Data were obtained using structured face-to-face interviews using the same protocol as was used at baseline. Each home-visit lasted for 2 to 3 h and was conducted either by one of three physiotherapists or by an occupational therapist, all of whom had clinical experience of neurological assessment and were trained for the purpose of data collection. Death certificates for the 32 PwMS who had died in the ten years since the baseline study were collected from the National Board of Health and Welfare with information about the date and cause of death. The Regional Ethical Review Board in Stockholm approved the study.

Information about use of immunomodulatory treatment and antidepressant drugs, civil status, level of education and work status was collected by interview. To assess coping capacity, the 13-item version of the sense of coherence scale (SOC) was used [11]. The data collectors assessed disease severity by using the EDSS [4]; in addition they assessed disease course. The assessments were verified by a senior neurologist (SF), as was the use of immunomodulatory treatment. Data about the time since diagnosis was collected at baseline from medical records. A 10-metre walking test was used to assess walking speed and was performed, with a turn, on a 5-metre course (the Timed 2 × 5 m walk test) [12]; a static start was used, the PwMS were instructed to walk as quickly as possible and the use of walking aids was documented. Manual dexterity was assessed with the Nine-Hole Peg Test (NHPT) for the right hand [13]. Cognitive function was assessed with the Mini-Mental State Examination (MMSE) [14] and the Symbol Digit Modalities Test (SDMT) [15]. The MMSE was used for screening of global cognitive performance. The SDMT assesses the capacity to direct attention quickly and accurately and was primarily administered with a written response; for those PwMS unable to write, the test was administered with an oral response. Disability in mood (depressive symptoms) was assessed using the Beck Depression Inventory II (BDI) [16]. The BDI consists of 21 items related to depression, each of which is self-assessed from 0 (absent) to 2 or 3 (severe). Dependency in personal and instrumental activities of daily living (ADL) was assessed with the Barthel Index (BI) [17] and the Katz Extended ADL Index (KE) [18], respectively, and frequency of social/lifestyle activities with the Frenchay Activities Index (FAI) [19]. The variables studied, instruments used and the criteria for the categorisation of variables are summarised in Table 1.

2.3. Statistical analysis

Descriptive statistics were used to present personal and disease-specific characteristics, and the presence of disability.

Due to non-normally distributed data, the Sign test was used for analyses of statistically significant changes in scores from baseline to the 10-year follow-up. Statistically significant changes in the proportion of PwMS with disability at baseline and at follow-up were analysed with the McNemar test. p value for changes was set to

Table 1
Variables studied, instruments used, and criteria for categorisation of the independent variables and the dependent variables used in the analyses of proportions with disability and in the analyses of predictors for increase in proportions with disability.

Variables and instruments	Categorisation criteria
Age	<51 years of age/≥51 years of age
Sex	Female/male
Coping capacity: Sense of Coherence Scale	Norm data from a reference group [20]. SOC weak: 13–54 points/SOC moderate or strong: 55–91 points
Education	Basic/high school or university
Time since diagnosis	≤10 years/>10 years
Disease severity: Expanded Disability Status Scale	EDSS mild: 0–3.5/EDSS moderate: 4.0–5.5/EDSS severe: 6.0–9.5
Disease course	Relapsing–remitting/progressive
Walking speed:Timed 2 × 5 m walk test[a]	Age- and sex-related norms [21]. Limitation: ≥−1 SD from average speed/no limitation: <−1 SD from average speed
Use of walking aid	Walk without aid/walk with aid/cannot walk
Manual dexterity: Nine-Hole Peg Test[b]	Norm data from a reference group [22]. Impairment: ≤0.5 peg/s/no impairment: >0.5 peg/s
Cognitive function: Mini Mental State Examination	Impairment: <28/no impairment: ≥28 [14]
Symbol Digit Modalities Test[c]	Age-related norms [15]. Impairment: ≥−1.5 SD from the mean/no impairment: <−1.5 SD from the mean
Mood: Beck Depression Inventory II	Depressive symptoms: ≥13/no depressive symptoms: <13 [8]
Activities of daily living:Barthel Index	Dependence: <100/independence: = 100
Katz ADL Index Extended	Dependence: <28/independence: = 28
Social/lifestyle activities: Frenchay Activities Index	Age- and sex-related norms [23]. Reduced frequency: <25th percentile/not reduced frequency: ≥25th percentile

[a] Speed calculation was set to 0 m/s for PwMS unable to walk.
[b] Speed calculation was set to 0 pegs/s for PwMS unable to perform the test.
[c] Speed calculation was set to 0 for PwMS unable to perform the test.

≤0.05. The analyses of changes in disability over time included those who survived at the 10-year follow-up.

Generalized Estimating Equations (GEE) were conducted to investigate the increase over 10 years, in the proportion of the PwMS with limitation in walking (use of walking aid), impaired cognition (SDMT), depressive symptoms (BDI), dependence in ADL (KE), and reduced frequency of social/lifestyle activities (FAI) from baseline to the 10-year follow-up (for categorisation of the dependent variables see Table 1). Independent variables at baseline were included in all the models, together with the time variable (0 and 10 years). The independent variables were age, sex, coping capacity, level of education, disease severity, disease course, time since diagnosis and mood. Since linearity in the logit scale could not be assumed, the independent variables were categorised. In the model with depressive symptoms as the dependent variable, mood was not included as an independent variable. Stepwise backward selection criteria were employed, entering all independent variables and then removing those variables with a p value > 0.05. For each dependent variable, one final model was created where all independent variables with a p value ≤ 0.05 were retained. Interactions between time and the independent variable were controlled for and when the interactions were significant the main effects were also retained in the final model irrespective of statistical significance. The results are presented as odds ratios (OR) with 95% CI and p values. In case of significant interactions, simple effects were presented, i.e. effect of one variable holding the other variable fixed.

In order to analyse the predictive value of different independent variables on mortality, regardless of cause of death, univariate Cox regression analyses were performed followed by a multivariate Cox regression using stepwise forward selection criteria. For the stepwise selection, the criterion for entry was set to a p value ≤ 0.05, and a p value ≥ 0.10 was used as the criterion for removal. The selection of the independent variables in the models was based on: 1) variables previously identified as predictors (age, sex, time since diagnosis, disease severity, disease course), and: 2) variables that have not been explored as predictors in previous studies (coping capacity, level of education, cognition and mood). The results are presented as hazard ratios with 95% confidence intervals (CI) and p values. The SPSS, version 20.0 (SPSS Inc., Chicago, Illinois, USA) and the SAS® System 9.1, SAS Institute Inc., Cary, NC, USA were used for the statistical analyses.

3. Results

Of the 166 PwMS included at baseline, 32 PwMS were deceased at the 10-year follow-up, 11 declined to participate, four were not able to be interviewed due to severe disability and one had not answered most of the questions and was, therefore, excluded. Consequently, a total of 118 PwMS were included in the analyses of changes in disability over 10 years.

Personal and disease-specific characteristics at baseline and at the 10-year follow-up are summarised in Table 2. The proportion of PwMS with immunomodulatory treatment had decreased from 41% to 21%, whereas the proportion of PwMS who used antidepressant drugs had increased from 10% to 27%. The proportion categorised as EDSS mild had decreased from 36% to 16%, and the proportion categorised as EDSS severe had increased from 44% to 65%. The proportion of PwMS categorised with a relapsing-remitting course had decreased from 48% to 21%.

Median EDSS scores had changed from 5.0 at baseline to 6.5 at the 10-year follow-up. The reasons for failing to complete the tests were inability due to MS and refusal. There were statistically significant changes (p value < 0.001) in median scores in all areas of functioning, implying worse functioning, except in mood (p value = 0.300).

The proportion of PwMS with disability at baseline and at the 10-year follow-up are presented in Table 3. There was an increase in the proportion of disabled PwMS from baseline to follow-up in all areas except in depressive symptoms, cognitive impairment assessed by the SDMT, and reduced frequency of social/lifestyle activities. Of those with depressive symptoms, six (29%) used anti-depressant drugs at baseline and five (22%) at follow-up. At baseline 17 (15%) could not walk at all and at follow-up 24 (21%). Of the 113 PwMS who participated in the timed 2 × 5 m walk test, 17 (15%) walked with an aid at baseline and 37 (33%) at follow-up, 79 (70%) walked without aid at baseline and 52 (46%) at follow-up.

The final GEE models for the dependent variables limitations in walking, impaired cognition, depressive symptoms, dependence in ADL and reduced frequency of social/lifestyle activities are presented in Table 4. Disease severity predicted an increase in proportion with disability in all dependent variables studied except depressive symptoms. The time effect variable was significant for predicting an increase in proportion with limitation in walking and dependence in ADL with an OR of 11.3 and 3.1 respectively from baseline to the 10-year follow-up. For limitation in walking, there was also a significant interaction between the time effect variable and "time since diagnosis" which was most pronounced for those with a shorter time since diagnosis (≤10 years) with an OR of 30.5. For dependence in ADL, the time effect variable interacted with "age" with an OR of 5.5 for those with an age ≥51 years. For reduced frequency of social/lifestyle activities the time effect variable interacted with "age" with an OR of 2.7 for those with an age ≥51 years. There was also an interaction between the time effect variable and "disease severity", with an OR

Table 2
Personal and disease-specific characteristics of people with MS at baseline and at the 10-year follow-up and p values for the changes in personal and disease-specific characteristics between baseline and follow-up n = 118.

	Baseline	Follow-up	p value
Mean age, years (SD)	49 (11)		
Female, n (%)	85 (72)		
Moderate or strong sense of coherence, n[a] (%)	96 (87)	95 (86)	0.842
High school or university education, n (%)	88 (75)	90 (76)	0.804
Working full- or part-time, n[b] (%)	62 (56)	37 (43)	0.055
Immunomodulatory treatment, n (%)	48 (41)	20 (21)	<0.001
Antidepressant drugs n (%)	12 (10)	27 (23)	<0.001
Time since diagnosis, mean (SD)	18 (11)		
Disease severity, n (%)[c]	41 (36)	19 (16)	<0.001
EDSS mild	24 (20)	22 (19)	0.750
EDSS moderate	51 (44)	77 (65)	<0.001
EDSS severe			
Relapsing–remitting disease course, n (%)	55 (48)	24 (21)	<0.001

[a] n = 110.
[b] Based on PwMS <65 years, n = 109 at baseline, n = 86 at follow-up.
[c] Mean EDSS 5.0 at baseline, 6.0 at follow-up.

Table 3
Proportions of people with MS with disability at baseline and at the 10-year follow-up, p values for changes in the proportion with each disability n = 118.

Test (range)	Baseline disability n (%)	Follow-up disability n (%)	p value
Timed 2 × 5 m walk test[a]	100 (85)	108 (91)	0.027
Nine-Hole Peg Test	65 (55)	77 (65)	0.014
Mini-Mental State Examination	41 (35)	68 (58)	<0.001
Symbol Digit Modalities Test[b]	49 (42)	48 (41)	1.000
Beck Depression Inventory[c]	21[d] (18)	23[e] (19)	0.823
Barthel Index	44 (37)	73 (62)	<0.001
Katz Extended ADL Index	71 (60)	87 (74)	0.002
Frenchay Activities Index[f]	66 (56)	73 (62)	0.345

[a] 113 (96%) completed the test at baseline and at follow-up.
[b] 105 (89%) completed the test at baseline and at follow-up.
[c] 113 (96%) completed the test at baseline and at follow-up.
[d] 6 PwMS used antidepressant drugs.
[e] 5 PwMS used antidepressant drugs.
[f] 117 (99%) completed the test at baseline and at follow-up.

Table 4
Estimated odds ratios (OR), 95% confidence intervals (CI) and p values for the predictive value of the time factor (0 and 10 year) and the independent variables on an increase over 10 years in proportion with limitation in walking, impaired cognition, depressive symptoms, dependence in activities of daily living and reduced frequency of social/lifestyle activities in people with MS according to the final[a] Generalized Estimating Equation models n = 118.

Dependent variable	Independent variable categorisation	OR (CI)	p value
Limitation in walking[b]	Time since diagnosis >10 years	1.9 (0.8–4.9)	ns
	Time since diagnosis ≤10 years	1 (ref)	
	Time 10-year follow up	11.3 (5.0–25.3)	<0.001
	Baseline	1 (ref)	
	≤10 years since diagnosis/time: 10-year follow-up	30.5 (6.6–140.3)	<0.001
	Baseline	1 (ref)	
	>10 years since diagnosis/time: 10-year follow-up	4.2 (2.4–7.2)	<0.001
	Baseline	1 (ref)	
	Moderate EDSS	6.9 (2.1–22.8)	0.002
	Mild EDSS	1 (ref)	
	Severe EDSS	194.7 (60.1–631.1)	<0.001
	Mild EDSS	1 (ref)	
Impaired cognition[c]	Male	2.5 (1.1–5.4)	0.023
	Female	1 (ref)	
	Moderate EDSS	2.9 (1.1–7.9)	0.036
	Mild EDSS	1 (ref)	
	Severe EDSS	3.1 (1.3–7.0)	0.008
	Mild EDSS	1 (ref)	
Depressive symptoms[d]	SOC weak	4.05 (1.38–11.85)	0.011
	SOC moderate or strong	1 (ref)	
Dependence in activities of daily living[e]	Age ≥51 years	1.4 (0.6–3.2)	ns
	Age ≥51 years	1 (ref)	
	Time 10-year follow up	3.1 (1.7–5.9)	<0.001
	Baseline	1 (ref)	
	Age <51 years/time: 10-year follow up	1.8 (0.9–3.6)	ns
	Baseline	1 (ref)	
	Age ≥51 years/time: 10-year follow-up	5.5 (2.1–14.7)	<0.001
	Baseline	1 (ref)	
	Moderate EDSS	5.2 (2.1–13.2)	<0.001
	Mild EDSS	1 (ref)	
	Severe EDSS	45.9 (13.6–154.3)	<0.001
	Mild EDSS	1 (ref)	
Reduced frequency of social/ lifestyle activities[f]	Age ≥51 years	0.9 (0.4–2.2)	ns
	Age <51 years	1 (ref)	
	Time 10-year follow up	1.3 (0.7–2.2)	ns
	Baseline	1 (ref)	
	Age <51 years/time: 10-year follow-up	0.6 (0.3–1.3)	ns
	Baseline	1 (ref)	
	Age ≥51 years/Time: 10-year follow-up	2.7 (1.1–6.9)	0.033
	Baseline	1 (ref)	
	SOC weak	3.4 (1.3–9.2)	0.015
	SOC moderate or strong	1 (ref)	
	Moderate EDSS	3.1 (1.2–8.0)	0.021
	Mild EDSS	1 (ref)	
	Severe EDSS	28.0 (9.4–83.7)	<0.001
	Mild EDSS	1 (ref)	
	Mild EDSS/time: 10-year follow-up	4.3 (1.5–12.4)	0.006
	Baseline	1 (ref)	
	Moderate EDSS/time: 10-year follow-up	1.5 (0.5–4.5)	ns
	Baseline	1 (ref)	
	Severe EDSS/time: 10-year ollow-up	0.3 (0.1–0.7)	0.004
	Baseline	1 (ref)	

[a] Independent variables and interactions with p values ≤ 0.05 were retained in the final models. When the interactions were significant the main effects also were retained in the final model irrespective of statistical significance.
[b] Timed 2 × 5 m walk test.
[c] Symbol Digit Modalities Test.
[d] Beck Depression Inventory.
[e] Katz Extended ADL Index.
[f] Frenchay Activities Index.

of 0.3 for reduced frequency of social/lifestyle activities for those with a severe EDSS at baseline.

Among the 32 deceased PwMS, mean age at the time of death was 63 years for women and 70 years for men. At baseline, median disease severity was EDSS 7.0, 27 PwMS had a progressive course, 12 were receiving immunomodulatory treatment, and 5 were receiving antidepressant drugs. Univariate analyses and the final model of the multivariate Cox regression analysis for the prediction of the independent variables of mortality are presented in Table 5. Age ≥51 years, severe EDSS and a progressive disease course were associated with mortality in the univariate analyses. Age ≥51 years and depressive symptoms were associated with mortality in the multivariate analyses. The estimated log-odds and the standard errors in the GEE analyses and in the multivariate Cox regression analysis were of reasonable magnitude and thus revealed no signs of collinearity.

The death certificates revealed that MS was an underlying cause of death for 16, and a contributing cause of death for seven of the 32 deceased PwMS. The underlying causes of death for the remaining 16 deceased PwMS were cancer, respiratory diseases, accidents, cardiovascular diseases, infectious diseases or other diseases.

Table 5
Hazard ratios, 95% confidence intervals (CI) and p values for the association between the independent variables on mortality in people with MS over the 10-year period according to univariate analyses and the final model of the multivariate Cox regression analyses (n = 155[a]).

Independent variable	Variable categorisation	Univariate analyses		Final model	
		Hazard ratio (CI)	p value	Hazards ratio (CI)	p value
Age	≥51 years of age	3.4 (1.5–7.6)	0.003	14.6 (1.5–14.4)	0.009
	<51 years of age	1		1	
Sex	Male	1.5 (0.7–3.6)	0.312		ns
	Female	1			
Sense of coherence	Weak	1.3 (0.4–4.5)	0.650		ns
	Moderate or strong	1			
Education	Basic	1.4 (0.7–3.0)	0.349		ns
	High school or university	1			
Time since diagnosis	>10 years	1.9 (0.9–4.1)	0.078		ns
	≤10 years	1			
Disease severity	EDSS severe	4.0 (1.4–11.6)	0.009		ns
	EDSS moderate	0.9 (0.2–4.9)	0.898		
	EDSS mild	1			
Disease course	Progressive	3.9 (1.5–10.1)	0.005	3.3 (0.9–11.5)	0.066
	Relapsing–remitting	1		1	
Cognition	Cognitive impairment	1.4 (0.6–3.0)	0.431		ns
	No cognitive impairment	1			
Mood	Depressive symptoms	1.8 (0.7–4.8)	0.204	2.7 (1.04–7.24)	0.041
	No depressive symptoms	1		1	

[a] The multivariate Cox regression analyses included all PwMS available at baseline except the 11 PwMS who declined to participate in the 10-year follow-up.

4. Discussion

This population-based longitudinal study demonstrated that disease severity (EDSS) and the proportion of PwMS with disability in walking, manual dexterity and personal and instrumental ADL increased over a 10-year period, but that the proportions with cognitive impairment, depressive symptoms and reduced frequency in social/lifestyle activities remained stable. Changes in median scores were found in all assessed areas except in mood.

In the final GEE models, disease severity (EDSS) predicted an increase in the proportion with disability in all assessed areas except the proportion with depressive symptoms at the 10-year follow-up. The time effect variable was significant for an increase in proportion with limitation in walking and dependence in ADL. Older age and depressive symptoms at baseline were associated with mortality over the 10-year period.

The mean change in disease severity (EDSS) over the 10-year period was one point, which is consistent with previous findings [3], and the mean change from EDSS 5.0 to 6.0 found in this study indicates the passing of an important milestone, i.e., the need for a walking aid [24]. Walking speed was reduced at baseline and was further impaired at follow-up. Severe EDSS at baseline predicted, as expected since the EDSS places significant emphasis on the ability to walk, an increased proportion with limitation in walking. The time effect variable was more pronounced for those PwMS with shorter time since diagnosis at baseline compared to those with longer time since diagnosis. A possible explanation for this result is that those with longer time since diagnosis at baseline already had limitation in walking. The high odds ratios in the model for limitation in walking imply an extremely high event rate for this outcome. Early rehabilitation that focuses on walking [25] is likely to preserve independence in ADL and frequency of social/lifestyle activities [26]. The proportion of PwMS with disability in manual dexterity increased to 65% at follow-up. This highlights that manual dexterity should also be thoroughly assessed and that studies on the effect of interventions that aim to sustain/improve manual dexterity are required [26].

The proportion of PwMS dependent in personal and instrumental ADL increased to 62% and 74% respectively. A more severe EDSS at baseline predicted an increase in this outcome which could be expected considering the association between walking and ADL [26]. It could also be expected that the time effect variable was significant only for those with an older age at baseline in predicting dependence in ADL since dependence in ADL increases with age. Interestingly, the time effect variable had an inverse effect on reduced frequency of social/lifestyle activities for those PwMS with a severe EDSS at baseline. There may be an adaptation process to the consequences of the disease over time, facilitated by personal factors such as moderate or strong SOC and/or facilitating environmental factors such as the use of healthcare services that enable participation in society despite increased disability [9].

Although the proportion of PwMS with cognitive impairment was stable over time according to the SDMT, a significant decrease in the raw score of the SDMT was seen. A possible explanation for this result can be that the raw score of the SDMT was compared to age-related norms. Both the proportion with cognitive impairment and the raw score of the MMSE significantly changed over time implying a decreased cognitive function. The SDMT is an instrument recommended for use in PwMS [35] while the result from the MMSE should be interpreted with greater caution due to its low sensitivity and specificity in PwMS [14]. Those PwMS with mild EDSS were more likely to remain cognitively intact than those with moderate and severe EDSS. A previous review stated that cognitive impairment encompasses all disease stages but there seems to be an association between increasing disability level and worse cognitive decline [5]. Male sex was also a predictor for an increase in proportion with cognitive impairment over time, which supports previous findings [27]. What clinical implications this might have, requires further study. In addition, considering the impact of cognitive impairment on working ability [28], further studies of the effectiveness of specific interventions, such as vocational rehabilitation, are needed.

The proportion of PwMS with depressive symptoms (almost 20%) was stable over the 10-year period. In this study a weak SOC was the only predictor of depressive symptoms, and the importance of coping capacity to manage depression among PwMS has been found in previous longitudinal studies [29]. Depressive symptoms in PwMS have been found to be undertreated pharmacologically [30], and PwMS experience a lack of psychological interventions [31]. There was an increased use of antidepressant drugs, though not among those with depressive symptoms, which could be explained by an increased treatment of, e.g., neurogenic pain. It is not known if those with depressive symptoms had access to other treatment, i.e., psychological interventions. The effort to detect and provide evidence-based care for depressive symptoms, therefore, needs to be continued. A care manager responsible for the support of, and continuous contact with the depressed person,

is recommended as a feasible model [32] and might also be effective in the care of PwMS. Recent studies of cognitive behavioural therapy for depressive symptoms in PwMS have shown promising results [33], but further studies are needed in order to conclude if this is a feasible method for PwMS regardless of concurrent disability [2]. Although depressive symptoms are considered to be functionally impairing [8], this was not confirmed in our analyses of predictors for limitation in walking, impaired cognition, dependence in ADL and reduced frequency of social/lifestyle activities.

Of the deceased PwMS, 72% had MS listed on their death certificate as an underlying or contributing cause of death. The remaining 28% died from cardiovascular disease, pulmonary infections and accidents. These causes may directly or indirectly be attributed to MS [34]. By underestimating MS as an underlying or contributing cause of death, important MS-related interventions to prevent secondary conditions, such as physical deconditioning, throughout the progress of the disease, may be neglected [25]. Depressive symptoms at baseline were associated with mortality over the 10-year period. Although this result needs to be confirmed in larger population-based studies, it highlights that health-care professionals need to be aware of the psychological aspects of the disease.

The instrument's sensitivity to change is a strength in the present study. However, some methodological limitations of this study are important to consider. By having only two points of data collection with ten years in between, we cannot take into account variations that might have occurred during this period and that could have affected the outcome in disability. It is possible that there is an underestimation of the real changes in disability and mortality in our follow-up sample considering that 30 PwMS included in the baseline study did not agree to participate, and there was a loss of 16 PwMS at follow-up. It is likely that reasons for not participating were, at least in some cases, related to disability. It is likely that the proportion of PwMS with disability in different assessed areas would have been higher, if those PwMS who died were included in the analyses of changes in disability over time. The results should therefore be interpreted with these limitations in mind. Since the number of participants in the GEE analyses and the multivariate Cox regression analysis were relatively low, the results need to be confirmed in larger population-based studies. The multiple testing of related outcomes in the GEE analyses increases the risk of Type I error. However, given the exploratory nature of these analyses, it was considered important to diminish the risk of Type II error, hence, the alpha level was not adjusted. Other areas of disability known to occur in PwMS (e.g., fatigue, bladder and bowel problems, loss of libido, speech and swallowing problems) [1] were not studied.

In conclusion, this study demonstrated that the proportion with disability in cognition, mood and in social/lifestyle activities remained stable over a 10-year period, while the proportion with disability in walking, manual dexterity and personal and instrumental ADL increased. The time effect variable was significant for outcomes of a more physical character. Disease severity, assessed by the EDSS, predicted disability in limitation in walking, impaired cognition and dependence in ADL, which indicates that the EDSS is a useful tool for predicting future disability in these areas. The high proportion with depressive symptoms and the possible association between depressive symptoms and mortality highlight the need for health-care professionals to consider the psychological aspects of the disease, and also that further studies of the suitability of, for example, cognitive behavioural therapy, are required. In order to organise individually tailored health-care, it is necessary to obtain a broader understanding of the health condition of PwMS over the course of a decade. Thus, future studies of, for example, the use of health-care and changes in health-related quality of life over the course of a decade, are necessary.

Conflict of interest

There are no conflicts of interest to report.

Acknowledgements

The authors wish to express their gratitude to all the PwMS for their participation in this study. The work was supported by the regional agreement on medical training and clinical research between Stockholm County Council and Karolinska Institutet, Doctoral School in Health Care Sciences at Karolinska Institutet and the Swedish Research Council (K2009-69X-21163-01-0).

References

[1] McAlpine D, Compston A. McAlpine's multiple sclerosis. Philadelphia, Pa: Churchill Livingstone/Elsevier; 2006.
[2] Johansson S, Ytterberg C, Claesson I, Lindberg J, Hillert J, Andersson M, et al. High concurrent presence of disability in multiple sclerosis. J Neurol 2007;254:767–73.
[3] Pittock SJ, Mayr WT, McClelland RL, Jorgenssen NW, Weigand SD, Noseworthy JH, et al. Change in MS-related disability in a population-based cohort: a 10-year follow-up study. Neurology 2004;62:51–9.
[4] Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology 1983;33:1444–52.
[5] Amato MP, Zipoli V, Portaccio E. Multiple sclerosis-related cognitive changes: a review of cross-sectional and longitudinal studies. J Neurol Sci 2006;245:41–6.
[6] Weinshenker BG, Bass B, Rice GP, Noseworthy J, Carriere W, Baskerville J, et al. The natural history of multiple sclerosis: a geographically based study. 2. Predictive value of the early clinical course. Brain 1989;112:1419–28.
[7] Kingwell E, van der Kop M, Zhao Y, Shirani A, Zhu F, Oger J, et al. Relative mortality and survival in multiple sclerosis: findings from British Columbia Canada. J Neurol Neurosurg Psychiatry 2012;83:61–6.
[8] Goldman Consensus G. The Goldman Consensus statement on depression in multiple sclerosis. Mult Scler 2005;11:328–37.
[9] World Health Organization. The international classification of functioning disability and health. Available at http://wwwwhoint/classifications/icf/en/; 2001. [Accessed November 2012.].
[10] Einarsson U, Gottberg K, von Koch L, Fredrikson S, Ytterberg C, Jin YP, et al. Cognitive and motor function in people with multiple sclerosis in Stockholm County. Mult Scler 2006;12:340–53.
[11] Antonovsky A. The structure and properties of the sense of coherence scale. Soc Sci Med 1993;36:725–33.
[12] van Herk IEH, Arendzen JH, Rispens P. Ten-metre walk, with or without a turn? Clin Rehabil 1998;12:30–5.
[13] Heller A, Wade DT, Wood VA, Sunderland A, Hewe RL, Ward E. Arm function after stroke: measurement and recovery over the first three months. J Neurol Neurosurg Psychiatry 1987;50:714–9.
[14] Beatty WW, Goodkin DE. Screening for cognitive impairment in multiple-sclerosis — an evaluation of the Mini-Mental State Examination. Arch Neurol 1990;47:297–301.
[15] Lezak MD. Neuropsychological assessment. New York: Oxford Univ. Press; 1995.
[16] Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry 1961;4:561–71.
[17] Mahoney FI, Barthel DW. Functional evaluation: the Barthel Index. Md State Med J 1965;14:61–5.
[18] Asberg KH, Sonn U. The cumulative structure of personal and instrumental ADL — a study of elderly people in a health-service district. Scand J Rehabil Med 1989;21:171–7.
[19] Wade DT, Legh-Smith J, Langton Hewer R. Social activities after stroke: measurement and natural history using the Frenchay Activities Index. Int Rehabil Med 1985;7:176–81.
[20] Langius A, Bjorvell H. Coping ability and functional status in a Swedish population sample. Scand J Caring Sci 1993;7:3–10.
[21] Oberg T, Karsznia A, Oberg K. Basic gait parameters — reference data for normal subjects, 10–79 years of age. J Rehabil Res Dev 1993;30:210–23.
[22] Wade DT. Measurement in neurological rehabilitation. Oxford: Oxford Univ. Press; 1992 .
[23] Turnbull JC, Kersten P, Habib M, Mclellan L, Mullee MA, George S. Validation of the Frenchay activities index in a general population aged 16 years and older. Arch Phys Med Rehabil 2000;81:1034–8.
[24] Confavreux C, Vukusic S. Age at disability milestones in multiple sclerosis. Brain 2006;129:595–605.
[25] Motl RW, Pilutti LA. The benefits of exercise training in multiple sclerosis. Nat Rev Neurol 2012;8:487–97.
[26] Kierkegaard M, Einarsson U, Gottberg K, von Koch L, Widen Holmqvist L. The relationship between walking, manual dexterity, cognition and activity/participation in persons with multiple sclerosis. Mult Scler 2012;18:639–46.
[27] Beatty WW, Aupperle RL. Sex differences in cognitive impairment in multiple sclerosis. Clin Neuropsychol 2002;16:472–80.
[28] Rao SM, Leo GJ, Ellington L, Nauertz T, Bernardin L, Unverzagt F. Cognitive dysfunction in multiple sclerosis II. Impact on employment and social functioning. Neurology 1991;41:692–6.
[29] Patten SB, Metz LM. Depression in multiple sclerosis. Psychother Psychosom 1997;66:286–92.
[30] Gottberg K, Einarsson U, Fredrikson S, von Koch L, Widén Holmqvist L. A population-based study of depressive symptoms in multiple sclerosis in Stockholm

County: association with functioning and sense of coherence. J Neurol Neurosurg Psychiatry 2007;78:60–5.
[31] Gottberg K, Einarsson U, Ytterberg C, Fredrikson S, von Koch L, Widén Holmqvist L. Use of health care services and satisfaction with care in people with multiple sclerosis in Stockholm County: a population-based study. Mult Scler 2008;14:962–71.
[32] Swedish Council on Health Technology Assessment. Support for psychiatric care in primary care. Available at: http://wwwsbuse/sv/Om-SBU/Nyheter/Implementeringsstod-for-psykiatrisk-evidens-i-primarvarden/ . [Accessed November 2012.].
[33] Beckner V, Howard I, Vella L, Mohr DC. Telephone-administered psychotherapy for depression in MS patients: moderating role of social support. J Behav Med 2010;33:47–59.
[34] Koch-Henriksen N, Bronnum-Hansen H, Stenager E. Underlying cause of death in Danish patients with multiple sclerosis: results from the Danish Multiple Sclerosis Registry. J Neurol Neurosurg Psychiatry 1998;65:56–9.
[35] Langdon D, Amato M, Boringa M, Brochet B, Foley F, Fredrikson S, et al. Recommendations for a Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS). Mult Scler 2012;18:891–8.